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DRAFT

NTP-CERHR EXPERT PANEL REPORT on REPRODUCTIVE and DEVELOPMENTAL TOXICITY of 1-BROMOPROPANE

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PREFACE

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1.0 CHEMISTRY, USAGE, AND EXPOSURE

1.1 Chemistry

1.1.1 Nomenclature

1-Brompropane: CAS=106-94-5
Synonyms: Propyl bromide; n-Propyl Bromide

1.1.2 Formula and Molecular Mass

Figure 1-1. Chemical Structure of 1-Bromopropane (1-BP)

C_3H_7Br mw=123.0

1.1.3 Chemical and Physical Properties

Table 1-1. Physicochemical properties of 1-BP

Property	Value
Boiling Point	71 C at 760 mm Hg
Melting Point	-110 C
Flashpoint	25.6 C*
Specific Gravity	1.353 at 20 C
Solubility in Water	2,450 mg/L
Vapor Pressure	110.8 mm Hg at 20 C
Stability	Stable*
Reactivity	Reacts with strong oxidizing agents and bases.*
Flammability	Flammable*
Log K_{ow}	2.10

Rev. in HSDB (2001), *Aldrich (1996)

1.1.4 Technical Products and Impurities

Two material safety data sheets reported the purity of 1-BP to be 99% (Aldrich, 1996; Fisher Scientific, 2000). One case study involving a >95% solution of 1-BP reported the contaminants of 1-BP as butyline oxide (<0.5%), 1,3-dioxolane (<2.5%), and nitromethane (<0.25%) (Sclar, 1999). The Occupational Safety and Health Administration (OSHA) analyzed samples of 1-BP and detected 2-bromopropane (2-BP) at concentrations ranging from 0.1-0.2% (OSHA, 1999). Table 1-2 lists ASTM (2000) standards for vapor-degreasing and general grade 1-BP.

Table 1-2. Specifications for Vapor-Degreasing Grade and General Grade 1-BP (ASTM, 2000).

Property	Specification	Test Method
Specific gravity, 25/25°C	1.320 to 1.350	D 2111
Distillation range (760 mm Hg)		D 1078
Initial boiling point, °C, min	70.0	
Dry point, °C, max	88.0	
Acidity (as HCl), weight %, max	0.0010	D2989
Alkalinity (as NaOH), weight %, max	0.020	D 2989
Water, weight %, max	0.0150	D 3401
Appearance	clear and free from suspended matter	D 3741
Color, APHA, max	15	D 2108
Free halogen	passes test	D 4755
Nonvolatile residue, weight %, max	0.0010	D 2109
Acid acceptance (as NaOH), weight %, min	0.15	D 2942
Aluminum scratch	passes test	D 2943
normal-propyl bromide content, weight %, min	93	GC
iso-propyl bromide content, weight %, max	0.1	GC

A tradename for 1-BP is AIBTA1 (O'Malley, 2001a).

1.2 Use and Human Exposure

1.2.1 Production Information

1-BP can be produced by the dehydration of propanol with bromine or hydrogen bromide in the presence of sulfur catalyst (Kim et al., 1999a). Manufacturers of 1-BP that are part of the Brominated Solvents Consortium include Albemarle Corporation, Dead Sea Bromine Group/Bromine Compounds Ltd. and Great Lakes Chemical Corporation (Huntingdon Life Science 2001). ATOFINA (formerly Elf Atochem) is also a manufacturer of 1-BP (ATOFINA, 2001). Additional manufacturers of 1-BP may include Diaz Chemical Corporation and Vineland Chemical Company (HSDB, 2001).

No information is available on the quantity of 1-BP produced in the United States at this time. Some U.S. companies have recently begun producing 1-BP and it is expected that demand for 1-BP will increase if it is used as a replacement for hydrochlorofluorocarbons (HCFCs) and methylene chloride (OSHA, 1999). OSHA projected that up to 240 million pounds of 1-BP could be produced annually if it remained unregulated and was used to replace chlorinated solvents such as trichloroethylene, perchloroethylene, and methylene chloride in vapor degreasing and cold metal cleaning operations. It is also expected that 1-BP could take over some of the market for HCFCs that currently have an annual consumption rate of 130 million pounds a year. In addition 2.5 million pounds of 1-BP could be used annually as a cleaning agent for machinery in manufacturing plants within 3 years.

Estimates on the potential market for 1-BP in the future were also submitted by Poly Systems USA, Inc (Ruckriegal, 2000). Although the Poly System estimates were lower than the OSHA estimates, they still indicate that 1-BP could become a high production volume chemical in the future. Poly Systems reported that up to 80 million pounds of 1-BP could used in metal cleaning operations, 10 million pounds in aerosols, and 55 million pounds in adhesives.

Some current uses of 1-BP may be limited in the future due to recommendations made by certain manufacturers. Albemarle has stated that use of 1-BP in adhesive and other applications in which 1-BP exposure cannot be controlled should be restricted or prohibited (O'Malley, 2001b). ATOFINA (2001) has decided not to market 1-BP for solvent applications.

1.2.2 Use

1-BP may be used as a solvent for fats, waxes, or resins or as an intermediate in the synthesis of pharmaceuticals, insecticides, quaternary ammonium compounds, flavors, or fragrances (HSDB, 2001). 1-BP is also used in spray adhesives (Reh, 2000) and as a cold vapor degreaser (Reh and Nemhauser, 2000). Potential uses for 1-BP in the future are discussed in the previous section.

1.2.3 Occurrence

General Population Exposure Sources

The general population could be exposed to 1-BP if it were present in air, water, food, or consumer products. There is very little information documenting the presence of 1-BP in such media. An unspecified level of 1-BP was detected in the drinking water from an unreported location (HSDB, 2001). Unreported levels of 1-BP were detected in the volatile emissions from household waxes, liquid pastes, and detergents (HSDB, 2001). 1-BP was also detected in six species of marine microalgae at unreported levels; it was postulated that the 1-BP was a product of monohalo and dihalo-oxo-fatty acid hydrolysis and that it could be transported from the algae to the marine environment (HSDB, 2001).

Occupational Exposures Sources

1-BP is being reviewed under the EPA's Significant New Alternatives Policy (SNAP) program for finding substitutes for ozone-depleting substances (EPA, 2000). Until occupational exposure limits are set, the EPA is recommending an 8-hour time weighted average (TWA) exposure limit of 50-100 ppm. Doull and Rozman (2001) recommended a TWA-threshold limit value of 60–90 ppm with a notation for skin absorption. Albemarle Corporation is recommending a TWA limit of 25 ppm (Reh and Nemhauser, 2000). ATOFINA (2001) is recommending an 8-hour occupational exposure limit value of 5 ppm.

NIOSH measured 1-BP levels in the breathing zones (personal samples) of workers in 2 plants where a 1-BP-containing spray adhesive was used in the manufacture of seat cushions (Reh, 2000). In the first plant, time weighted average (TWA) exposures in 69 workers ranged from 60-381 ppm with a mean of 169 ppm. TWA exposures in 16 workers from the second plant ranged from 18-254 ppm with a mean of 96 ppm. NIOSH also measured 1-BP concentrations in a plant where 1-BP was used as a cold degreaser in the presence of a local exhaust system (Reh and Nemhauser, 2000). Personal samples were obtained from 20 employees who worked in the area of the degreaser. Time weighted averaged 1-BP exposures exceed the minimal quantification limit of 0.02 ppm in 7 workers and ranged from 0.04–0.63 ppm.

Exposures to workers could occur through dermal contact and inhalation of vapors.

1.2.4 Human Exposure

1.3 Utility of Data

1.4 Summary of Human Exposure Data

Within the United States 1-BP is known to be used as a solvent in spray adhesives (Reh, 2000) and as a cold vapor degreaser (Reh and Nemhauser, 2000). 1-BP may also be used as a solvent for fats, waxes, or resins or as an intermediate in the synthesis of pharmaceuticals, insecticides, quaternary ammonium compounds, flavors or fragrances (HSDB, 2001). In the future it is possible that 1-BP may be used as a substitute for hydrochlorofluorocarbons (HCFCs). Two manufacturers of 1-BP are recommending that 1-BP not be used in solvent applications in which exposures cannot be controlled (O'Malley, 2001b; ATOFINA, 2001). No information was found that documents exposure of the public to 1-BP through contact with air, drinking water, food, or consumer products. 1-BP levels were measured in three occupational settings. In two plants where 1-BP was being used as a spray adhesive, time weighted average (TWA) exposures of 60-381 ppm 1-BP and 18-254 ppm 1-BP were measured in the breathing zones of 69 and 16 workers, respectively (Reh, 2000). In a plant where 1-BP was used as vapor degreaser within a local exhaust system, 7 of 20 workers in the area had personal TWA exposures (0.04-0.63 ppm) that exceeded the minimal quantification limit of 0.02 ppm.

2.0 GENERAL TOXICOLOGICAL AND BIOLOGICAL PARAMETERS

2.1 Toxicokinetics and Metabolism

No human toxicokinetics or metabolism data were identified.

Empirical evidence from rodent toxicity studies indicates that 1-BP is absorbed by the inhalation route. However, animal studies that characterize and quantify absorption and distribution of 1-BP by any route were not found. The blood:air partition coefficients for humans (7.08) and rats (11.7) indicate that 1-BP is readily soluble in blood (Meulenberg and Vijverberg, 2000). The studies described below discuss metabolism and excretion of 1-BP.

Kim et al. (1999a) examined the inducibility of Cytochrome P450 isoenzymes and other related enzymes in microsomes of 7-week-old male and female Sprague-Dawley rats that inhaled 50, 300, or 1,800 ppm/kg 1-BP (analytical grade) for 6 hours/day, 5 days/week, for 8 weeks. It was verified that units of concentration were ppm and not ppm/kg (Kim, 2001). Chamber concentrations of 1-BP were monitored by gas chromatography (GC) every 15 minutes. Enzyme activities were studied in 10 rats/sex/group. [Methods of statistical analyses were not discussed]. 1-BP treatment resulted in significantly increased activities of NADH b_5 reductase and p-nitrophenol hydroxylase (pNPH) in high dose males and females. Western blot analysis from 1-BP treated rats revealed a strong signal for CYP2E. Glutathione S-transferase (GST) activity significantly increased in male rats of all dose groups [Expert Panel notes that no dose-related increase was observed] and female rats in the two highest dose groups. Glutathione peroxidase activity was significantly increased in all treated rats. Lipid peroxides (LPO) were significantly increased in females of the two highest dose groups and males in the highest dose group. In most cases, enzyme activities were higher in male versus female rats. The authors made the following conclusions about the metabolism of 1-BP: (1) metabolic mechanism of 1-BP is sex-dependent, (2) the CYP2E1 isoenzyme is possibly responsible for 1-BP metabolism, (3) free radicals are produced by activated intermediates as halide radicals, and (4) GST is involved in detoxification and protection of tissues against oxidative damage induced by halide radicals.

Strength/Weaknesses: This study demonstrates a concentration-related increase in metabolic enzyme activity that may be important in the activation or deactivation of 1-BP. Sufficient numbers of animals were used, and the methodology for enzyme assays was adequately described. However, conclusions concerning the metabolism of 1-BP by these enzyme pathways appear to be unsupported.

Utility (Adequacy) for CERHR Evaluation Process: The data are adequate to provide some indication of alterations in metabolism in response to exposure to 1-BP.

Kaneko et al. (1997) studied the *in vitro* metabolism of 1-BP in hepatic microsomes of male Wistar rats by measuring the rate of substrate disappearance and rate of product (n-propyl alcohol) formation. The authors demonstrated that there were 2 sets of Vmax and Km metabolic constants. According to authors, differences in rate between substance disappearance and n-propyl alcohol formation suggested the possibility of alternate pathways besides metabolism of 1-BP to n-propyl alcohol or that n-propyl alcohol is further metabolized. The procedures and results for this experiment were reported in the form of a short communication.

Strength/Weaknesses: This study provides information on the metabolism of 1-BP by microsomal enzymes (likely cytochrome P-450). In addition, there is a clear indication of 2 enzymatic pathways, both of which have reasonable affinity for 1-BP, but a low capacity for metabolism.

Utility (Adequacy) for CERHR Evaluation Process: The data demonstrate that 1-BP is metabolized by microsomal enzymes, although to a minor extent. This information may be important in assessing risk for general toxicity since metabolism from mixed function oxidase (MFO) enzymes is likely to not play a significant part in activation of 1-BP to active metabolites.

Khan and O'Brien (1991) incubated isolated rat hepatocytes in the presence of 100 μM 1-BP or six other 1-bromoalkanes for up to 1 hour and measured intracellular glutathione levels. 1-BP caused a time-related reduction in glutathione level. The magnitude of glutathione depletion was directly related to the chain length of the bromoalkane. Incubation with 1-BP resulted in minimal decreases (32% lower than untreated cells) in intracellular glutathione levels compared with long-chain bromoalkanes (88% lower than untreated cells).

Strength/Weaknesses: This is a well-designed study that provides direct evidence that 1-BP can react with glutathione and deplete GSH levels in the cell.

Utility (Adequacy) for CERHR Evaluation Process: In progress.

Barnsley et al. (1966) fed 4 male rats (age and strain unspecified) a diet containing ^{35}S-labelled yeast for 3 days, injected 2 of the rats subcutaneously with 1 ml of 40% w/v solution of 1-BP [purity not specified] in arachis oil on the fourth day, collected urine for the 24 hours after dosing, and measured metabolites in urine by radiochromatography. Three metabolites were detected in the urine of treated but not control rats: n-propylmercapturic acid, 2-hydroxypropylmercapturic acid, and n-propylmercapturic acid sulphoxide.

Strength/Weaknesses: Although this study lacks the analytical sophistication that is common to current studies, it provides direct evidence of conjugation and excretion of 1-BP with glutathione presumably via glutathione-S-transferases.

Utility (Adequacy) for CERHR Evaluation Process: This study is important in understanding the value of glutathione-S-transferases (GST) pathway in the metabolism of 1-BP. GST activation is an important part of haloalkane metabolism and toxicity. For some haloalkanes, biotransformation to an active metabolite leads to long-term effects. However, there is no indication that active metabolites are produced in quantities that lead to long-term effects. In fact, the data from this study suggest that GST activation is minimal compared with other haloalkanes.

Jones and Walsh (1979) further characterized metabolites of 1-BP in rats. Male Sprague-Dawley rats [230-260 g; age and number treated not specified] were treated orally with 1-BP [purity not specified] in arachis oil at 200 mg/kg bw/day for 5 days and the urine was pooled and examined by thin layer chromatography. Three mercapturic acid compounds identified in urine were the same as those identified by Barnsley et al. (1966): N-acetyl-S-propyl-cysteine, N-acetyl-S-(2-hydroxypropyl)cysteine, and N-acetyl-S-propylcysteine-S-oxide. Three additional compounds were also identified in urine: N-acetyl-S-(3-hydroxypropyl)cysteine, N-acetyl-S-(2-carboxyethyl)cysteine, and 3-bromopropionic acid. *In vitro* metabolism studies with 1-BP demonstrated that oxidation of C_3 and C_2 occurs before conjugation of the alkyl group with glutathione. Figure 2-1 illustrates the possible metabolic pathway of 1-BP determined by Jones and Walsh (1979).

Jones and Walsh (1979) studied the excretion of 1-BP in the expired air and urine of Sprague-Dawley rats following a single I.P. injection with 200 mg/kg. Initial excretion of unchanged 1-BP in expired air was rapid with 56% and 60% exhaled after 2 and 4 hours respectively. Only trace amounts were detected in expired air after 4 hours. Twenty-five percent of the administered bromide was excreted in urine over a period of 100 hours.

Strength/Weaknesses: This study further characterizes the metabolism of 1-BP, demonstrating the exhalation of a significant amount of unmetabolized 1-BP following exposure. On the other hand, details on the methodology are unclear with numbers of animals used not specified.

Utility (Adequacy) for CERHR Evaluation Process: The value of this study is to define the metabolic pathway of 1-BP and identify intermediate metabolites. This information will help in assessing potential long-term health effects.

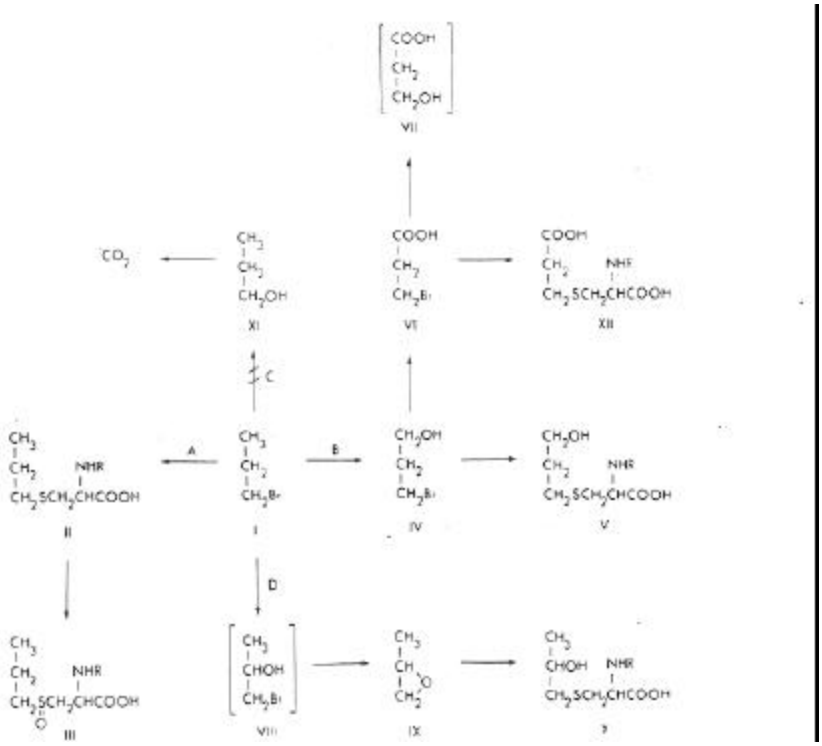

Figure 2-1. Possible metabolic pathway for 1-BP in the rat. Compounds in parentheses were not isolated in urine. Copied from Jones and Walsh (1979).

2.2 General Toxicity

2.2.1 Human Data

Sclar (1999) published a case study of a 19-year-old male who experienced weakness of the lower extremities and the right hand, numbness, and difficulty swallowing and urinating after a 2 month occupational exposure to a degreasing and cleaning solvent. The solvent consisted primarily of 1-BP (95.5%) and also butylene oxide (<0.5%), 1,3-dioxolane (<2.5%), and nitromethane (<0.25%). Levels of exposure were not measured and it is not clear by which route exposure occurred. Although the patient wore gloves (material unspecified), the skin on his right (preferentially exposed) hand darkened, suggesting that the gloves may not have offered

sufficient protection. Nerve conduction tests revealed prolonged distal motor and F response latencies with slower extremity sensory nerve conduction velocities but preserved amplitude response. Magnetic resonance imaging (MRI) scans revealed patchy areas of increased T_2 signal in the periventricular white matter and root enhancement in the lumbar region of the spinal cord. An analysis of spinal fluid did not detect antibodies for infectious agents. According to the author, the evidence suggested that the patient was suffering from a symmetric demyelinating polyneuropathy with central nervous system involvement. Because similar symptoms were observed in rats exposed to 1-BP, the author hypothesized that the patient's symptoms may have resulted from 1-BP exposure.

Strength/Weaknesses: This study reports information on effects in humans that mimic the effects observed in rodents; however, the evidence is from a single individual without exposure information or demonstration that personal protective equipment (PPE) was not used.

Utility (Adequacy) for CERHR Evaluation Process: This study provides some evidence in humans of effects observed in animals. However, because it is only a case-report involving a single individual, less weight is given to this study as true evidence of effects in humans.

In 1998, NIOSH conducted a health hazard evaluation at a plant where a 1-BP-containing spray adhesive was used in the manufacture of seat cushions (Reh, 2000). Forty-three employees (34 females and 9 males) provided a blood sample for a CBC count and answered a medical questionnaire. Individuals were 18-64 years of age (mean 31 years). Based on industrial hygiene data, 1-BP exposures in those employees were categorized as 'low' (117 ppm), 'medium' (170 ppm), or 'high' (197 ppm). NIOSH concluded that there were no CBC abnormalities related to individual or categorical exposure. The employees in the high exposure group reported having headaches at least once a week. NIOSH stated that the headaches could have been related to 1-BP exposure but noted the lack of an exposure-response trend since the lower exposure groups reported a similar frequency of headaches. The questionnaire also included questions about reproductive function that are discussed under Section 4.

Strength/Weaknesses: This study evaluates hematology data in humans from a cohort of workers whose exposure to 1-BP is known. It is possible to compare, directly, these results with animal data. A weakness of the study is that only a few individuals (43 of 70) completed the survey, and that raw data were not presented for hematology. The investigators should have compared the exposure data between those who completed the survey and those who didn't to gauge potential selection bias. In addition, pre-exposure hematology values for these individuals is not available to ascertain if exposure resulted in changes.

Utility (Adequacy) for CERHR Evaluation Process: The value of this study is that effects on hematology were assessed and can be compared with animal data. Unfortunately, no raw data were presented. The authors indicate that there is no correlation of reduced erythrocyte count and exposure. Although there was a suggestion of an exposure-response gradient with respect to low red blood cell count, the small numbers of subjects and lack of an unexposed comparison group reduce the utility of the preliminary study.

2.2.2 Animal Data

Acute oral and dermal toxicity studies of 1-BP (Elf Atochem, 1993; 1995b) were located, but are not reported because they were not considered to have utility for the evaluation of reproductive or developmental effects.

An acute inhalation toxicity study of 1-BP (Elf Atochem, 1997) was conducted using 7-9 week old male and female Wistar rats obtained from Charles River France (SPF, WISTAR Crl rats: (WI) BR). The study was conducted according to Good Laboratory Practices. In a limit test, 5 rats/sex/group were exposed to 0 or 34.6 g/m^3 [34, 600 mg/m^3]. In the main part of the study, 5 males and 5 females/group were exposed to 0, 30.2, 35.1, 37.0, or 42.5 g/m^3 [30,200, 35,100, 37,000, or 42,500 mg/m^3] 1-BP (99.5%). Five satellite males/group were exposed to 0 or 36.4 g/m^3 [36,400 mg/m^3] and blood was collected 24 hours and 13 days after exposure for hematology. All exposures were conducted for 4 hours in a nose-only chamber (flow-past system). Concentrations were verified by gas chromatography. Animals were observed for 14 days following treatment. Body weights were measured daily. Lungs and testes from control animals and those exposed to 34.6 (males only) and 42.5 g/m^3 were weighed and examined microscopically [tissue fixed in 10% formalin]. All animals exposed to 37.0 and 42.5 g/m^3 died on test. Most animals exposed to 35.1 g/m^3 died (7/10) and some animals exposed to 34.6 g/m^3 died (3/10). The LD50 was estimated at 35.0 g/m^3. Clinical signs included respiratory distress and "general weakness." Surviving animals gained weight over the 14 days. There was an increase in leukocyte count, hemoglobin, and packed cell volume on Day 2 for the 36.4 g/m^3 group [no statistical evaluation], but these differences resolved by Day 14. There was no apparent change in relative testis weight and no microscopic testicular lesions in animals exposed to 1-BP. Pulmonary lesions consisting of edema and "emphysema" were observed in the 1-BP exposed animals.

Strength/Weaknesses: This study reports the findings of acute exposures to very high concentrations of 1-BP. Adequate numbers of animals were used and procedures conform to current standards and practices. A weakness of the study is the use of 10% formalin for fixation of the testes. This fixative is recognized as inadequate to properly evaluate subtle effects on the testes.

Utility (Adequacy) for CERHR Evaluation Process: This study demonstrates the acute toxicity of 1-BP under conditions of exposure that are directly comparable to other substances. The addition of testicular weight and histopathology is helpful in ascertaining if dramatic effects occur following acute exposure.

Kim et al. (1999b) studied the acute and repeated inhalation toxicity of 1-BP in 11- week-old male and female Sprague-Dawley rats (SPF grade, from Dae Han Laboratory Animal Research Center). In both parts of the experiment, rats inhaled reagent grade 1-BP and concentrations within chambers were monitored and confirmed by gas chromatography every 15 minutes (dynamic exposure conditions). For the acute study, five rats/sex/group inhaled 0, 11,000, 13,000 15,000, or 17,000 ppm [55,337, 65,398, 75,460, or 85,521 mg/m^3] 1-BP for 4 hours. Rats were observed for 2 weeks following exposure. Clinical signs of toxicity in treated groups during exposure included piloerection, reduced activity, ataxia, lacrimation, and reduced response to noise. One female in the 13,000 ppm group and 4 females and 2 males in the 15,000 ppm group died within 24 hours. All rats in the 17,000 ppm group died within an unspecified time period. An LC_{50} of 14,374 ppm (95% confidence limit: 13,624-15,596 ppm) was calculated. The lowest lethal concentration was <11,833 ppm and the LC_{100} was >18,186 ppm. At the end of the observation period, all surviving rats were sacrificed by carbon dioxide and necropsied; abnormal tissues were examined histologically. Cytoplasmic vacuolation of hepatocytes surrounding the central vein was observed in an unspecified number of treated rats but the effect was not dose-dependent.

In the repeated inhalation portion of the Kim et al. (1999b) study, 10 rats/sex/group inhaled 0, 50, 300, or 1,800 ppm 1-BP [252, 1509, or 9055 mg/m^3] for 6 hours/day, 5 days/week, for 8 weeks. [The rational for dose selection was not discussed]. Body weight and feed consumption were measured twice per week. Urine samples were collected over a 24 hour period prior to termination. At termination [animals were apparently terminated 24 hours after the last exposure], rats were sacrificed, blood was collected under anesthesia, and hematology, clinical biochemistry, and urinalysis tests were conducted. Data were analyzed by two-way analysis of variance (ANOVA) and Duncan's multiple t-test. Thymus, adrenal, testis, heart, lung, kidney, spleen, liver, and brain were weighed and fixed in 10% neutral buffered formalin, stained with hematoxylin-eosin or and or PAS-hematoxylin, and examined histologically. Clinical signs of toxicity included reduced activity and mild ataxia in the 1,800 ppm rats during exposure. Body weight gain was reduced in males and females of the high dose group (1,800 ppm), but food intake was not affected. Some statistically significant changes in hematological, blood chemistry, and urinalysis parameters were noted in treated rats. The authors stated that most values were within normal ranges but did not specify which values were outside normal limits. Minimal effects on hemoglobin, hematocrit, and red blood cell values were observed for the high-dose group; [the Expert Panel considered the toxicological significance of these effects to be unclear]. Significant decreases in some serum biochemistry values were observed, [these are considered by the Expert Panel to be of no toxicological significance]. Significant increases in male relative organ weights were noted for the left adrenal (≥50 ppm), liver and brain (≥300 ppm), and the right kidney and both testes (1,800 ppm). In the 1,800 ppm females, significant increases in relative organ weights were noted for ovaries, kidneys, and liver; thymus weight was significantly reduced at 50 and 1,800 ppm. [The Expert Panel noted that body weight was reduced for the 1,800 ppm group; this may have contributed to the increase in relative testicular and brain weights.] Histopathological evaluations revealed cytoplasmic vacuolation of hepatocytes surrounding the central vein in all treated animals, but the effect was not dose dependent. Renal tubular casts were seen in females of the 1,800 ppm group. There were no lesions observed in the other organs, including testes. The Expert Panel agreed with the authors' conclusion about lack of biological significance for hematology, blood chemistry, and urinalysis findings. A NOAEL of 300 ppm was selected by the Expert Panel.

Strength/Weaknesses: These studies used an adequate number of animals in a well-designed experiment. The details of exposure are adequate to assess how the exposures were conducted, and the inhalation procedures conform to standard practices. A weakness is the lack of clarity as to when animals were terminated following the last exposure, and how many days of exposure preceded necropsy.

Utility (Adequacy) for CERHR Evaluation Process: This study demonstrates the acute and subchronic toxicity of 1-BP under conditions of exposure that are directly comparable to other substances. There is a clear dose-response for effects, and histopathologic findings can be correlated with serum biochemistry. The study is judged to be adequate for use in the evaluation process.

Two additional repeated-exposure studies were conducted by a producer of 1-BP: a 28-day repeated exposure study (ClinTrials, 1997a) and a 13-week repeated exposure study (ClinTrials, 1997b). Both studies were conducted according to Good Laboratory Practices. In the 28-day study, male and female 6-week old Sprague-Dawley CD rats (Crl:CD(SD)BR; Charles River Canada Inc., St. Constant, Quebec) were divided into 4 groups of 10 animals/sex/group and exposed to 0, 2.0, 5.0, or 8.0 mg/L [2000, 5000, or 8000 mg/m^3] 1-BP for 6 hours/day, 5 days/week for 4 consecutive weeks [concentrations confirmed by IR spectrometry]. Purity of the 1-BP was >99% (O'Malley, 2001a). Exposure concentrations were selected on the basis of a 10-

day range-finding study. Animals were observed daily, and functional tests for neurotoxicity were performed prior to study start and termination. Body weight and feed consumption was measured weekly. Ophthalmologic examination was performed prior to study start and termination. Urine samples were collected overnight prior to sacrifice. At termination, blood was collected for hematology and clinical biochemistry. [There is no indication of how many exposures were conducted in the days preceding necropsy.] Brains and respiratory system from all dose groups and all tissues from the control and 8.0 mg/L groups were examined microscopically. Data were analyzed for homogeneity using a Bartlett's test. Homogeneous data were analyzed using an ANOVA followed by a Dunnett's test. Heterogeneous data were analyzed using a Kruskal-Wallis tests followed by a Dunn's test. Nearly all males (8/10) and a few females (3/10) exposed to 8.0 mg/L died or were sacrificed in a moribund condition. Animals in the 5.0 mg/L group showed clinical signs of toxicity. An abbreviated functional observational battery revealed impaired gait (ataxia and hypotonic gait) in the 8.0 mg/L group. No neurotoxicity was seen in the other groups. Body weight and feed consumption was significantly lower for the 8.0 mg/L group. No ophthalmologic findings were reported. Hematology for the 8.0 mg/L male group could not evaluated because only 2 animals survived, but decreased erythrocyte count, hemoglobin, and hematocrit values were seen for the 7 surviving females in the 8.0 mg/L group. Erythrocyte count and hemoglobin levels were significantly decreased for the male and female 5.0 mg/L groups. Females in the 5.0 mg/L group also had lower hematocrit values. [The Expert Panel concluded that no toxicologically significant changes were seen in serum biochemistry or urinalysis]. Relative weights (to body weight) of the liver, lungs, and kidneys were higher for the 5.0 mg/L male group compared with the controls. [The organ weights for the 8.0 mg/L male group could not be evaluated by the Expert Panel because of the high mortality]. Relative weights of the liver, spleen, thyroid/parathyroid glands, and kidneys were significantly higher for the 5.0 and 8.0 mg/L female groups compared with the controls. Females in the 8.0 mg/L group also had increased relative lung, and brain weights, and lower thymic weight. Microscopic evaluation indicated vacuolation of the brain for all treated groups. Vacuolation of the spinal cord and lesions of the kidneys and urinary tract and nasal cavity were seen in the high-dose animals. Lesions in the bone marrow thymus, spleen, and lymph nodes of high dose animals may have been related to treatment The two surviving males in the high-dose had aspermatogenesis [testes fixed in Zenker's fluid]. No ovarian lesions were observed at the high dose.

Strength/Weaknesses: These studies used an adequate number of animals in a well-designed experiment. The details of exposure are adequate to assess how the exposures were conducted, and the inhalation procedures conform to standard practices. Testes were fixed in an appropriate fixative for evaluation. A weakness is the lack of clarity as to when animals were terminated following the last exposure, and how many days of exposure preceded necropsy. An additional weakness is that the majority of tissues from the low- and mid-dose groups were not evaluated for histopathology.

Utility (Adequacy) for CERHR Evaluation Process: This study demonstrates the subchronic toxicity of 1-BP under conditions of exposure that are directly comparable to other substances. There is a clear dose-response for effects, and histopathologic findings can be correlated with serum biochemistry. The study is judged to be adequate for use in the evaluation process.

A 13-week repeated exposure study (ClinTrials 1997b) was conducted in which male and female 7–7.5-week old Sprague-Dawley CD rats (Crl:CD(SD)BR; Charles River Canada Inc., St. Constant, Quebec) were divided into 5 groups of 15 animals/sex/group and exposed to 0, 0.5, 1.0, 2.0, or 3.0 mg/L [500, 1000, 2000, or 3000 mg/m^3] 1-BP for 6 hours/day, 5 days/week for 13 consecutive weeks [concentrations monitored by IR spectrometry and confirmed by gas

chromatography]. Purity of 1-BP was >99% (O'Malley, 2001a). Exposure concentrations were selected based on the results of the 28-day study. Animals were observed daily, and functional tests for neurotoxicity were performed prior to study start and during Weeks 4, 8, and 13. Body weight and feed consumption was measured weekly. Ophthalmologic examination was performed prior to study start and termination. Urine samples were collected overnight prior to sacrifice. At termination, blood was collected for hematology and clinical biochemistry. [There is no indication of how many exposures were conducted in the days preceding necropsy.] All tissues from the control and high-dose groups were examined microscopically; respiratory tissues and tissues with lesions were examined at all doses. Data were analyzed for homogeneity using a Bartlett's test. Homogeneous data were analyzed using an ANOVA followed by a Dunnett's test. Heterogeneous data were analyzed using a Kruskal-Wallis tests followed by a Dunn's test. No clinical signs were observed that could be ascribed to 1-BP. No evidence of neurotoxicity was apparent. No differences in body weight were noted; feed consumption was significantly lower for the high-dose female group only during Weeks 3 and 4. No ophthalmologic findings were reported. No toxicologically significant effects were seen in hematology, clinical biochemistry, or urinalysis. A concentration-related increase in relative liver weight was seen for males with the liver weight of the 3000 mg/m^3 group significantly greater than for controls. No effect was seen for female rats. Microscopic evaluation indicated centrolobular vacuolation of the liver for the 2000 mg/m^3 and 3000 mg/m^3 male groups. No testicular or ovarian effects were noted [testes fixed in Zenker's fluid]. The study authors identified a no observed effect level (NOEL) of 1.0 mg/L (1000 mg/m^3) based on liver histopathology.

Strengths/Weaknesses: In Progress.

Utility (Adequacy) for CERHR Evaluation Process: In progress.

Several studies have evaluated the potential neurotoxicity of 1-BP.

In a short communication, Yu et al. (1998) reported the results of a study in which 10-week old male Wistar rats (9 per group from Shizuoka Laboratory Animal Center) were exposed to a concentration of 1000 ppm [5031 mg/m^3] 1-BP (99.4% purity) or filtered air in a chamber for 8 hours/day for up to 7 weeks as a companion group for a study of 2-BP. Exposures were conducted 7 days/week under dynamic conditions (Yu, 2001). This study was reported in greater detail by Yu et al. (2001). The exposure concentrations were monitored and confirmed by gas chromatography. Parameters examined included motor nerve conduction velocity (MCV), distal latency (DL), and histopathology. Hematology was examined in 5 rats/group. Organs examined histologically included testis, epididymis, prostate, seminal vesicle, femur, liver, kidney, heart, lung, thymus, brain, and sciatic or tibial nerves. Data were analyzed by ANOVA followed by the Tukey-Kramer multiple comparison method. By the 5th week of exposure, six of 9 treated animals demonstrated altered locomotor activity with paddle-like gait and hindlimb paralysis. All treated animals exhibited hind-limb paralysis by the 6th week of exposure. Because the treated rats began showing signs of paralysis and emaciation, four exposed animals were sacrificed following 5 weeks of exposure, and the remaining 5 plus 5 unexposed controls were sacrificed after 7 weeks. MCV was significantly reduced in exposed animals, and there was degeneration of peripheral nerves particularly of the myelin sheath. Evidence of central nervous system damage was also apparent. A histopathological evaluation of the nervous system revealed degeneration of the peripheral nerve and axonal swelling in the gracilis of the spinal cord. No histopathological effects were noted in the testis (fixed in Bouin's solution and stained with periodic acid-Schiff's reagent), liver, kidney, or bone marrow, and there were no changes in hematology. Serum creatine kinase was significantly reduced in exposed animals. The authors concluded that 1-BP is

more toxic to the nervous system but less toxic to the reproductive and hematopoietic system than 2-BP.

Strength/Weaknesses: A strength of this study is that appropriate methods were used for histopathologic evaluation of the nervous system and testes. A weakness is that the numbers of animals evaluated was minimal although it was deemed adequate to draw conclusions.

Utility (Adequacy) for CERHR Evaluation Process: This study provides good histopathologic evidence for neurotoxic effects and the lack of testicular effects.

Ichihara et al. (2000a) conducted a study to examine the dose- and duration- neurotoxicity response to 1-BP exposure. Eleven, 10-week-old male Wistar rats/group (from Shizuoka Laboratory Animal Center) were exposed to air or 200, 400, or 800 ppm [1006, 2012, or 4025 mg/m^3] 1-BP vapors for 8 hours/day for 12 weeks. Exposures were conducted 7 days per week under dynamic conditions (Yu, 2001). The highest dose was based on preliminary studies that noted debilitation of rats exposed to 1,000 ppm. Chamber concentrations were measured by gas chromatography. Neurological function was tested in 9 rats/group at weeks 0, 4, 8, and 12. Data were analyzed using one-way ANOVA followed by Dunnett's method. Mean body weights for the 400 and 800 ppm groups were significantly lower than controls after 8 weeks of exposure. Significant decreases in hindlimb grip strength were observed for all groups at 4 weeks, and for the 800 ppm group at 8 and 12 weeks. Hindlimb grip strength was also decreased for the 400 ppm group at 12 weeks. Significant decreases in forelimb grip strength were seen for the 400- and 800-ppm groups at 8 weeks, and for the 800-ppm group at 12 weeks. MCV was reduced for the 800-ppm group at weeks 8 and 12, and distal latency (DL) was increased for this group at weeks 4, 8, and 12. The rats in the 800 ppm group also displayed weak kicking and an inability to stand on a slope. At sacrifice, brain weight and blood chemistry were analyzed from 9 animals per group. Two animals per group were perfused for neurohistopathology. The weights of the cerebrum and gastrocunemius muscle were significantly reduced for the 800-ppm group. No differences in weight were seen for other parts of the brain or soleus muscle. Plasma creatinine phosphokinase activities for the 400- and 800-ppm groups were significantly reduced compared with controls. No changes were seen in the activities of lactate dehydrogenase, aspartate transaminase, alanine transferase, or alkaline phosphatase. Serum cholesterol was reduced is a dose-dependent manner, and plasma total protein and albumin were increased in a dose-related manner. Significant differences were seen for the 400- and 800-ppm groups. Globulin levels were also significantly increased for the 800-ppm group. Morphological evidence of neurotoxicity was only noted in the high dose group (800 ppm) and included ovoid or bubble-like debris in myelin sheaths of peripheral nerves, swelling of preterminal axons of the gracile nucleus, and irregular banding of soleus muscle fibers. Authors noted that reductions in grip strength could not be explained by nervous system effects and explained that grip strength represents total vital factors in limb function. In comparing the result of this study to those obtained in a preliminary study with 2-BP, the authors concluded that 1-BP is a more potent neurotoxin than 2-BP and is potentially neurotoxic to humans. The Expert Panel has determined the NOAEL to be 200 ppm.

Strength/Weaknesses: Concentration-related changes were observed in a thorough study of neurotoxicity. A weakness is that the numbers of animals evaluated was minimal although deemed to be sufficient for adequate conclusions to be drawn.

Utility (Adequacy) for CERHR Evaluation Process: The data adequately define neurotoxicity in animals exposed to high concentrations of 1-BP. This information is useful to assess potential human toxicity data.

Zhao et al. (1999) conducted a study to compare the neurotoxicity of 1-BP, 2-BP, and 2,5-hexanedione (2,5-HD) administered separately to rats. Seven to nine, male Wistar rats/group (age not specified; from Seiwa Experimental Animal Institute) were injected s.c. with each chemical in olive oil once/day, 5 days/week, for 4 weeks. Doses administered were 3.7 or 11 mmol/kg bw 1-BP [455 or 1353 mg/kg bw]; 1.1, 3.7, or 11.0 mmol/kg bw 2-BP [135, 455 or 1353 mg/kg bw]; and 2.6 mmol/kg bw 2,5-HD [296 mg/kg bw]. Purity of all chemicals was >97%. A control group of 9 rats was injected with the olive oil vehicle. According to the study authors, doses of 1.1, 3.7, and 11 mmol/kg bw are calculated to be equivalent to doses received by inhalation of 100, 300, and 1,000 ppm BP over an unspecified time period. Calculations were based upon respiratory data reported in a study by Mauderly et al. (1979). Bodyweights were measured weekly. MCV and motor latency (ML) were measured every two weeks using an electrophysiological method. Data were analyzed by one-way ANOVA followed by Duncan's multiple range test. Body weight gain in the 11 mmol 1-BP/kg bw group was lower compared to the control group. By 2 weeks of exposure, the MCV began decreasing in treated rats and reached statistical significance in the 11 mmol 1-BP/kg bw group at week 4. Increases in ML occurred but were not statistically significant. All three compounds, 2-BP, 1-BP, and 2,5-hexanedione, produced qualitatively similar responses in MCV and ML. The authors concluded that 1-BP and 2-BP were equally potent and both compounds were less potent than 2,5-hexanedione.

Strength/Weaknesses: This study utilizes a positive control (2,5-hexanedione) for comparison of motor nerve conduction velocity and latency. Sufficient numbers of animals are used for comparison, and varying dose levels were used to establish a dose-response. A weakness is the calculation of the dose to be administered based on calculations for inhalation of vapors in laboratory animals. In the absence of pharmacokinetic information, these can only be best estimates of absorbed dose. Based on previous information indicating that a significant amount of 1-BP is exhaled unmetabolized, the calculated amounts of absorbed dose may be overestimated.

Utility (Adequacy) for CERHR Evaluation Process: The utility of this study for the evaluation process is unclear. Although there are interesting data provided, the basis for dose selection cannot be verified. Therefore, the value of this study is unclear.

Fueta et al. (2000) reported a short communication of a study of changes in neuronal excitability in the brain of Wistar rats exposed to 1-BP for 6 hours/day, 5 days per week for up to 4 weeks (under dynamic conditions). A total of 30, 6-week old male rats were exposed to 1,500 ppm [7546 mg/m^3] 1-BP vapors [purity not specified] or air (n=14-16/exposure condition) for 6 hours/day, 5 days/week for 1, 3, or 4 weeks. Some animals exposed for 4 weeks were allowed to recover for 1 week prior to termination. This study is a follow-up to one reported by Ohnishi et al (1999) [Not available in English]. Transverse hippocampal slices were prepared following exposure for 1, 3, and 4 weeks and following a 1 week recovery period in rats exposed for 4 weeks. The brain slices were incubated in artificial cerebrospinal fluid during the stimulation of neurons and measurement of paired-pulse population spike (PS) responses in the granule cell layer of the dentate gyrus. When 2 pulses separated by a 10 msec interval were applied, a strong depression of the second PS was observed in control rats, but a nearly complete 2^{nd} PS response was seen in the 1-BP-treated rats. Paired pulse ratios (PPR) were calculated by dividing the 2^{nd} PS by the 1^{st} PS at interpulse intervals (IPI) ranging from 5-1,000 msec. PPRs significantly increased in all treated rats when interpulse intervals ranged from 5-20 seconds. At interpulse intervals ranging from 500-1,000 msec, significant increases in PPRs were only observed in rats exposed to 1-BP for 4 weeks, with and without the 1-week recovery period although the

magnitude of the difference after recovery was lower. Ataxic gait and convulsions were observed in the rats during the 4th week of exposure. The authors concluded that changes in the central nervous system (dentate gyrus), in conjunction with peripheral nerve damage, may explain neurobehavioral changes. The authors imply that effects were observed in the testes, although no data are presented.

Strength/Weaknesses: This study reports on time-related changes in the central nervous system that can be correlated with behavioral changes in animals. A strength of the study is that the exposure regimen conforms to standard practices, although details of monitoring the chamber concentrations were lacking. Another weakness is that no dose-response information is available.

Utility (Adequacy) for CERHR Evaluation Process: The adequacy of these data to the evaluation process is unclear. Effects were observed in the central nervous system before alterations in behavior were seen. Thus the correlation of CNS effects with behavioral changes is lacking. There is some evidence for a recovery process.

In a study that focused on reproductive toxicity, Ichihara et al. (2000b) exposed 10-week-old male Wistar rats to 0, 200, 400, or 800 ppm [1006, 2012, or 4025 mg/m^3] 1-BP vapors for 8 hours/day for 12 weeks (8-9 animals per group). The exposure concentrations were monitored and confirmed by gas chromatography. Exposures were conducted 7 days per week under dynamic conditions (Yu, 2001). Body weight gain was reduced in the 400 and 800 ppm groups. Significant changes in organ weight included increased relative liver weight (400 and 800 ppm) and absolute liver weight (800 ppm), and decreased absolute spleen weight (800 ppm). Histological effects observed in the livers of rats in the 800 ppm group included scanty spots in the cytoplasm of cells that were possibly glycogen, and reduced number and size of fat droplets around the central vein. There were no histopathological effects on the other non-reproductive organs examined (adrenal, thymus, spleen, lungs, heart, pituitary and kidney). The only significant hematological effects noted were increased mean corpuscular volume at 800 ppm and decreased mean corpuscular hemoglobin concentration at 400 and 800 ppm. Blood chemistry was not evaluated. A detailed description of reproductive findings and other study details is included in Section 4. The Expert Panel determined the NOAEL to be 200 ppm.

Strength/Weaknesses: This study provides dose-response information for effects on the male reproductive tract. A weakness is that the numbers of animals evaluated was minimal although adequate to draw conclusions.

Utility (Adequacy) for CERHR Evaluation Process: This study is the first time the authors have identified effects on the male reproductive tract.

2.3 Genetic Toxicity

Barber et al. (1981) examined the mutagenicity of 1-BP in *Salmonella* strains TA1535, TA1537, TA1538, TA98, and TA100 with and without S9 metabolic activation using a closed, inert incubation system designed to test volatile compounds. Five concentrations ranging from 1.1-20.3 umole/plate were tested in a total of 5 replicates. Positive controls included methyl-N-nitro-N'-nitrosguanidine, 2-aminoanthracene, 9-aminoacridine, and picrolonic acid. Negative control cultures were incubated without the addition of any chemicals. 1-BP treatment increased the mutation frequency in strains TA1535 and TA100 with and without metabolic activation. It does not appear that cytotoxicity was achieved at the highest concentration. Negative results were obtained in all other strains. Authors noted that for 1-BP the closed method of testing is a superior technique for assessing mutagenicity in volatile compounds because previous testing

according to the standard plate method gave negative results.

Strength/Weaknesses: This study provides information of genetic toxicity in relevant strains of bacteria. The study was well-conducted and used techniques for exposure of vapors. There are no perceived weaknesses.

Utility (Adequacy) for CERHR Evaluation Process: The study provides evidence that 1-BP can induce mutations with or without metabolic activation. It is of interest that mutagenic events were observed only in strains TA1535 and TA100, and not in other strains. Strains TA100 and TA1535 are known to possess nascent GST activity (Graves et al., 1994; Thier et al., 1993) which may be linked to the mutations observed.

Elf Atochem (1996) examined the mutagenicity of 1-BP in L5178Y mouse lymphoma cells. The cells were treated in duplicate for 3 hours with 125-1500 mg/L 1-BP (99.3% purity) in the absence of metabolic activation or 125-2500 mg/L 1-BP with S9 activation. The vehicle, dimethylsulfoxide (DMSO), was used as a negative control. Methylmethane sulfonate and cyclophosphamide were used as positive controls. A reproducible two-fold increase in mutation rate compared to the negative control and/or evidence of a dose relationship were considered a positive response. Two separate experiments were conducted. In the absence of metabolic activation, a reproducible increase in mutation frequency was observed in cells treated with 1000-1500 mg/L 1-BP in both experiments. No increase in mutation frequency was observed in the first experiment with S9 activated cells. However, in the second experiment with S9 activated cells, an increase in mutation frequency was noted at 1500-2000 mg/L 1-BP. All cells died after treatment with 2500 mg/L 1-BP. Study authors concluded that this study demonstrated mutagenic activity, especially in the absence of S9 activation.

Strengths/Weaknesses: In progress.

Utility (Adequacy) For CERHR Evaluation Process: In progress.

Elf Atochem (1995a) conducted a micronucleus study of 1-BP in mice. In the initial study, male and female Swiss OF1/ICO:OF1 (IOPS Caw) mice from Iffa Credo were treated twice with 0, 100, 400, or 800 mg/kg 1-BP (99.3%) in corn oil by ip injection. Cyclophosphamide was used as a positive control. At least 5 animals/sex/group were used. Animals were killed 24 hours after the last treatment. The initial toxicity study indicated that 800 mg/kg would be a suitable high dose, and a second study was conducted with 0 and 800 mg/kg 1-BP. Mortality in males during the second study prompted a third study using an additional dose level of 600 mg/kg for males. Only the 600 mg/kg males and 800 mg/kg females were evaluated because the polychromatic/normochromatic erythrocyte (PE/NE) ratio for the controls from the initial attempt (100, 400, 800 mg/kg) were outside of the historic range and the test was considered to be invalid. No increase in micronucleated erythrocytes was observed in males treated with 600 mg/kg and females treated with 800 mg/kg. The positive control group did demonstrate a significant increase in micronucleated erythrocytes.

Strength/Weaknesses: This study provides information of the lack of genetic toxicity *in vivo*. The study was well-conducted and there are no perceived weaknesses.

Utility (Adequacy) for CERHR Evaluation Process: The study provides evidence that 1-BP does not cause chromosomal damage *in vivo*.

2.4 Carcinogenicity

No carcinogenicity studies were identified.

2.5 Summary of General Toxicology and Biological Effects

Toxicokinetics

No information concerning the toxicokinetics of 1-BP in humans was found. Evidence from animal data indicates that 1-BP is absorbed following inhalation exposure. The blood:air partition coefficient indicates that 1-BP is readily soluble in blood (Meulenberg and Vijverberg, 2000). However, a major portion of absorbed 1-BP is exhaled (excreted in the expired air) unchanged (Jones and Walsh, 1979). Metabolism of 1-BP can occur through the MFO system (Kim et al., 1999a) and via conjugation with glutathione (Barnsley et al., 1966; Jones and Waslsh, 1979). The available data suggest that metabolism via MFO enzymes is slow and may be easily saturable. Conjugation with glutathione can occur either enzymatically or non-enzymatically producing several cysteine conjugates that are excreted in the urine. Whether glutathione S-transferases are involved in the activation of 1-BP to a reactive species is unclear, although the data from mutagenicity tests suggests that such activation can occur (Barber et al., 1981; Graves et al., 1994; Their et al., 1993). This suggests that conjugation with glutathione and glutathione S-transferases plays a role in the toxicity of 1-BP.

General Toxicity

Limited data of toxicity in humans were found. One case report indicated peripheral neuropathy in a worker exposed to a degreasing and cleaning solvent containing 95.5% 1-BP (Sclar, 1999). While animal data indicate similar effects following prolonged exposure to high concentrations of 1-BP, the lack of exposure data for the case-report make conclusions difficult. NIOSH conducted a survey of workers exposed to 1-BP dividing them into groups of low (117 ppm), medium (170 ppm), or high (197 ppm) exposure (Reh, 2000). No effects were associated with exposure.

Animal data indicate that the acutely lethal concentration is >30,200 mg/m^3 (Elf Atochem, 1997). There may be a difference in the LC_{50} for Wistar rats compared with Sprague-Dawley rats (Kim et al., 1999b). Repeated exposure to concentrations of > 2000 mg/m^3 result in adverse effects to the central nervous system, possibly striated muscle, and liver (Ichihara et al., 2000a). CNS and muscular effects are associated with ataxia, altered gait, and decreased grip strength. Liver effects are defined by vacuolation in male rats, but with little other evidence of adverse effect. This suggests that the liver changes may be adaptive. Respiratory effects have been observed following exposure to high concentrations (>30,000 mg/m^3) (Elf Atochem, 1997). These include pulmonary edema and changes to the nasal mucosa. Testicular effects have been reported and will be discussed in the section on Reproductive toxicity. No effect levels of 1000-1500 mg/m^3 have been reported. Table 2-1 summarizes NOELs and effects observed in animal general toxicity studies.

Genetic Toxicity

The genetic toxicity of 1-BP has been tested in *S. typhimirium* strains TA98, TA100, TA1535, TA1537, and TA1538 (Barber et al., 1981). Positive results were reported only for TA100 and TA1535. These strains are known to possess GST activity that may result in the metabolism of 1-BP to a reactive metabolite (Graves et al., 1994; Their et al., 1993). Because direct evidence of such a reactive metabolite are not available, this hypothesis is purely speculative. A mouse

micronucleus test of 1-BP was negative (Elf Atochem, 1995a). Positive results were obtained in a mutagenicity assay in L5178Y mouse lyphoma cells (Elf Atochem, 1996).

Carcinogenicity

There are no data available on the carcinogenicity of 1-BP in humans or animals.

Table 2-1. Summary of General Toxicity Effects in Inhalation Studies

Concentration (mg/m^3)	**Exposure Regimen**	**Species/ strain**	Dose: Effect	**Reference**
30,200 35,100 37,000 42,500	4h/1d; nose-only	Wistar rat	**NOEL = 30,200 mg/m^3.** 35,100 mg/m^3: Mortality in 3/10. 37,000 mg/m^3: Mortality in 10/10.	Elf Atochem, 1997
55,337 65,398 85,521	4h/1d; whole-body	Sprague-Dawley rat	**NOEL = 55, 337 mg/m^3.** **65,398 mg/m^3:** Mortality in 1/10. **85,521 mg/m^3:** Mortality in 10/10.	Kim et al, 1999b
2,000 5,000 8,000	6h/5d/4wk; whole-body	Sprague-Dawley rat	**2,000 mg/m^3:** Vacuolation of the brain. **5,000 mg/m^3:** ↓RBC, hemoglobin, hematocrit; ↑ relative liver, spleen, thyroid/parathyroid, and kidney weights; vacuolation of the brain. **8,000 mg/m^3:** Mortality (8/10; 3/10 F), ataxia and hypotonic gait; vacuolation of brain and spinal cord; kidney lesions; Aspermatogenesis.	ClinTrials, 1997a
252 1509 9055	6h/5d/8wk; whole-body	Sprague-Dawley rat	**NOAEL = 1509 mg/m^3.** **1509 mg/m^3:** ↑ relative liver and brain weight. **9055 mg/m^3:** Ataxia, ↓ activity, ↓ body weight gain, ↑ relative kidney, liver, ovaries, and testes weight; renal tabular casts; cytoplasmic vacuolation of hepatocytes surrounding the central vein of all treated animals (not dose dependent).	Kim et al, 1999b
500 1000 2000 3000	6h/5d/13wk; whole-body	Sprague-Dawley rat	**NOEL = 1,000 mg/m^3.** **2,000 mg/m^3:** Centrolobular vacuolation of the liver. **3,000 mg/m^3:** ↑ relative liver weight and centrolobular vacuolation of the liver.	ClinTrials, 1997b
5,031	8h/7d/7wk; whole-body	Wistar rat	Hind-limb paralysis, paddle-like gait, degeneration of myelin sheath of peripheral nerves, ↑ creatine kinase activity, degeneration of peripheral nerve, axonal swelling of gracilis of the spinal cord; ↓ MCV.	Yu et al, 1998; 2001
1,006 2,012 4,025	8h/7d/12wk; whole-body,	Wistar rat	**NOEL = 1,006 mg/m^3.** **2,012 mg/m^3:** ↓ Body weight; ↓ hind-limb grip strength; ↓ creatinine phosphokinase activity; ↑ relative liver weight. **4,025 mg/m^3:** ↓ Bodyweight; ↓ fore-limb and hind-limb grip strength; ↓ motor nerve conduction velocity; ↑ distal latency; ↑ relative and absolute liver weight, ↓ spleen weight; ↓ creatinine phosphokinase activity; ovoid or bubble-like debris in myelin sheaths of peripheral nerves, swelling of preterminal axons of the gracile nucleus, and irregular banding of soleus muscle fibers; cytoplasmic spots in liver.	Ichihara et al, 2000a

↑=Increased Effect, ↓=Decreased Effect; M=males; F=Females

3.0 DEVELOPMENTAL TOXICITY DATA

3.1 Human Data

3.2 Experimental Animal Toxicity

The brominated solvents consortium sponsored a standard developmental toxicity study using Crl: CD (SD) IGS BR Sprague-Dawley rats (Huntingdon Life Sciences, 2001). Pregnant animals (25/group) were exposed to vapor concentrations of 0, 100, 498, or 996 ppm (500, 2500, or 5000 mg/m^3) 1-BP (99.9% purity) for 6 hours/day from gestation day 6-19. Exposures were conducted in whole-body chambers under dynamic conditions. Concentrations were monitored by infra red (IR) spectrometry. Exposure concentrations were selected to result in a gradation of toxic effects with some toxicity at the highest dose and no toxicity at the lowest dose. Pregnancy was terminated on gestation day 20 and the fetuses removed by caesarean section. The uterine contents were weighed and one-half the fetuses preserved in Bouin's fluid for soft-tissue evaluation, while the other half were eviscerated and processed for skeletal evaluation using Alizarin Red-S and Alcian Blue. Continuous data were analyzed by ANOVA, Dunnett's test, and/or the Kruskal-Wallis test and incidence data were analyzed by a Fisher Exact Test with Bonferonni correction. The study was conducted according to Good Laboratory Practices (GLP). Results of this study are summarized in Table 3-1. There was no effect on pregnancy rate. One animal from the 996 ppm group was sacrificed moribund. Examination of this animal indicated extramedulary hematopoiesis, hepatocellular necrosis, hepatocellular inflammation, lymphoid cell hyperplasia of the spleen. These findings were not considered to be treatment related. Lacrimation and salivation were observed in animals exposed to 996 ppm. Mean bodyweight and bodyweight corrected for gravid uterus weight for the 498 ppm and 996 ppm groups were significantly lower than for controls; weight gains and food intake were also significantly reduced in these two groups. No embryotoxicity was observed, and no treatment-related visceral or skeletal anomalies were noted. Fetal body weight was significantly reduced in all treated groups. There was a dose-related increase in the litter incidence of reduced ossification at 498 ppm and 996 ppm. The authors associated this finding with maternal toxicity and reduced fetal body weight. A significant increase in the litter incidence of bent ribs was seen in the 996 ppm group, but the authors felt that this may be a common finding in untreated rats. [The Expert Panel considers the high incidence in the 996 ppm group, and dose-related increase from 498 ppm to 996 ppm to suggest that bent ribs were treatment related.] The authors identify 500 mg/m^3 as a NOEL for maternal and fetal toxicity, and 996 ppm for teratogenicity. [The Expert Panel believes that a concentration of * mg/L is an appropriate NOEL for teratogenicity based on…].

Strength/Weaknesses: This is a well-conducted developmental study performed in accordance with current regulatory guidelines and standard practices. Exposures are well-defined and monitored. Fetuses were evaluated for developmental effects using the appropriate methods. There are no obvious weaknesses.

Utility (Adequacy) for CERHR Evaluation Process: These data are directly applicable to the evaluation process in that they provide information from a standard study in animals.

Table 3-1. Major Effects Observed in a Prenatal Toxicity Study by Huntingdon Life Sciences (2001).

Number[a]	Dose (ppm)	Maternal Effects	Fetal Effects
25/23	0		
25/23	100	NOEL	↓ Fetal weight (4.8%).
25/25	498	↓ Weight gain and food intake.	↓ Fetal weight (4.8%). ↑ Litters with reduced ossification (17 vs 4%).
25/24	996	↓ Weight gain and food intake. Clinical signs.	↓ Fetal weight (7.3%). ↑ Litters with reduced ossification (18 vs 4%). ↑ Litters with bent ribs (13 vs 0%). No increases in prenatal mortality, sex distribution, or external, skeletal, or visceral malformations.
Protocol: CD rats were exposed to 1-BP on gd 6-19. Dams were sacrificed on gd 20 for evaluation of prenatal toxicity. **Notes:** ↑,↓=Statistically significant increase, decrease. [a]Number of pregnant dams/litters evaluated.			

Limited information about developmental toxicity associated with exposure to 1-BP is available from a 2-generation reproductive toxicity study in which Crl:CD(SD) IGS BR rats were exposed to 0, 100, 250, 500, or 750 ppm [0, 503, 1257, 2514, 3771 mg/m^3] 1-BP vapors during premating, mating, gestation, and lactation (WIL Research Laboratories, 2001). Complete details of this study are included in Section 4. Statistically significant decreases in live litter size were observed in F_0 and F_1 females exposed to 500 ppm and no offspring were observed in F_0 females exposed to 750 ppm. Given that there were proportionate decreases in implantation sites in these females, the Expert Panel noted that the plausible explanation is an effect on fertility rather than adverse effects on fetal development. Significant decreases in litter weight gain during nursing occurred in F_1 males and F_2 males and females of the 500 ppm group. There were no treatment-related effects on postnatal survival in either F_1 or F_2 litters. The authors stated that skeletal examinations would be conducted according to the Dawson method if external abnormalities were observed. There were no reports of external malformations in offspring.

Strength/Weaknesses: This is a well-conducted study performed according to standard practices and guidelines. Adequate numbers of animals were used in the evaluation and all the appropriate endpoints for reproductive toxicity were examined. The most obvious weakness is that developmental effects may have been missed because animals were allowed to give birth which prevents examination of fetuses for anomalies or for gestational mortality.

Utility (Adequacy) for CERHR Evaluation Process: This two generation study provides convincing evidence that adverse effects on reproductive performance were due to reduced fertility; no evidence of developmental toxicity was found in pregnant females (through 500 ppm groups). This study provides useful indirect evidence that 1-BP is not a developmental toxicant through 500 ppm, at least not from implantation (day 5) through gestation, and does not produce adverse developmental defects through weaning.

Limited information about developmental effects, is available from a range-finding study conducted by Huntingdon Life Sciences (1999) and sponsored by the Brominated Solvents Consortium. Ten Crl: CD (SD) IGS BR rats/group were randomly assigned to groups and exposed to air or 1-BP vapors (99.9% purity) at concentrations of 100, 199, 598, or 996 ppm [503, 1,001, 3,008, 5,010 mg/m^3] on gd 6-19 for 6 hours/day. Dams delivered and were exposed to 1-BP together with their litters on pnd 4-20. Concentrations in chambers were verified. At birth, pups form 7-9 litters/group were sexed, weighed, and examined for viability and external abnormalities. Pub growth and survival was monitored from birth through weaning. At weaning, 1 pup/sex/litter was randomly selected for a post-weaning growth study and exposed to 1-BP on pnd 22-29. Hematology and clinical chemistry analyses and organ weight measurements were conducted in dams at the end of the lactation period and offspring from the pnd 22-29 day post-weaning study on pnd 29. Data were analyzed by ANOVA, , Dunnett's test, and/or the Kruskal-Wallis test. The study was conducted according to Good Laboratory Practices (GLP). Results in this study are summarized in Table 3-2. Dams in the 996 ppm group experienced lacrimation and increased salivation. Maternal body weight gain was reduced during treatment in the 199, 598, and 996 ppm groups but did not reach statistical significance. Food intake was not affected by treatment. Significant organ weight changes in dams included increases in relative weights (to body weight) of the liver and kidneys in the 598 and 996 groups. The authors did not consider any changes in hematology or clinical chemistry to be toxicologically significant in dams. No external abnormalities or reduced birth weight was reported. During the period from birth to weaning, no increased pup mortality was observed; pup body weights were slightly but not significantly reduced in the 996 ppm group. Body weight gain during the post-weaning period (pnd 22-29) was significantly lower for males in the 598 and 996 groups and females in the 996 group. Significant organ weight changes in male offspring included increased absolute adrenal (100 and 199 ppm) and reduced brain weight (996 ppm) and increased relative adrenal weight (100, 199, and 996 ppm). In female offspring, absolute brain weight was significantly reduced in the 996 ppm group. The only hematological and biochemical effects in offspring that were considered to be treatment related by authors included statistically significant reductions in platelet levels in 598 and 996 ppm females and 996 ppm males, elevations in gamma-glutamyl transferase levels in 996 ppm males and females, and reduced glucose levels in the 996 ppm females and all treated males (significant only at high dose for males). Authors identified a maternal NOEL of 100 ppm but did not identify a developmental NOEL. The Expert Panel noted that exposure to 1-BP during the postweaning period reduced body weight gain and may have targeted adrenals, platelets and liver.

Strength/Weaknesses: In progress.

Utility (Adequacy) for CERHR Evaluation Process: In progress.

Table 3-2. Major Effects Observed in a Developmental Range-Finding Study by Huntingdon Life Sciences (1999).

Number[a]	Dose (ppm)	Maternal Effects	Offspring Effects
10/8	0		
10/9	100	No effects.	↑ Relative adrenal weight (M).
10/8	199	No effects.	↑ Relative adrenal weight (M).
10/7	598	↑ Relative liver and kidney weight.	↓ Bodyweight gain on pnd 22-25(M). ↓Platelets (F).
10/10	996	↑ Relative liver and kidney weight. Clinical signs. No toxicologically significant effects on hematology or blood chemistry	↓ Bodyweight gain on pnd 22-29 (M) and 22-25 (F). ↑ Relative adrenal weight (M) ↓Absolute brain weight ↓ Platelets. ↓ Glucose levels. ↑Gamma-glutamyl transferase. No reduced birth weight, external abnormalities or increased mortality.

Protocol: CD rats were exposed to 1-BP on gd 6-19. Dams delivered and were then exposed to 1-BP with litters on pnd 4-20. One offspring/sex/litter was exposed on pnd 22-28.
Notes: ↑,↓=significant increase, decrease. M,F=Males, Females only.
[a]Number of pregnant dams/litters evaluated.

3.3 Utility of Data

3.4 Summary of Developmental Toxicity

There were no studies located that address developmental toxicity in humans exposed to 1-BP.

There is evidence to indicate that inhalation exposure to 1-BP in rats causes developmental toxicity in rats. A prenatal developmental toxicity study in rats observed decreased fetal weight and reduced ossification at ≥500 ppm (≥2500 mg/m^3) and increased bent ribs at 996 ppm (5000 mg/m^3); decreased maternal weight gain and food intake also occurred at these doses (Huntingdon Life Sciences, 2001). No teratogenic effects were seen at inhalation doses up to 996 ppm (5000 mg/m^3) 1-BP on gd 6-19. Two studies examined postnatal growth in rat pups whose dams were exposed to 1-BP during gd 6-19 (Huntingdon Life Sciences, 1999) or the entire gestation and lactation period (WIL Research Laboratories, 2001). Postnatal pup body weight gain was reduced in litters from dams exposed to 3008 mg/m^3 (598 ppm) (Huntingdon Life Sciences, 1999). F_1 and F_2 pup weight gain was reduced during the nursing period at a dose of 2514 mg/m^3 (500 ppm) in a 2-generation study in rats (WIL Research Laboratories, 2001). Additional relevant effects in pups are listed in Table 3-3.

Table 3-3. Summary of Developmental Toxicity in Inhalation Studies

Concentration (mg/m^3)	Exposure Regimen	Species/ Strain	Dose: Effect[a]	Reference
500 2500 5000	6h/d gd 6-19	CD Rat	**Dams:** **Maternal NOAEL=500 mg/m^3** **2500 mg/m^3:** ↓ Weight gain and food intake. **5000 mg/m^3:** ↓ Weight gain and food intake; clinical signs. **Fetuses:** **Developmental NOAEL=500 mg/m^3** **2500 mg/m^3**: ↓ Bodyweight; ↓ossification. **5000 mg/m^3**: ↓ Bodyweight; ↓ossification;↑bent ribs.	Huntingdon Life Sciences, 2001
503 1001 3008 5010	6h/d gd 6-19	CD Rat	**Dams:** **Maternal NOAEL=503 mg/m^3** **1001 mg/m^3**: ↓ Bodyweight gain. **3008 mg/m^3**: ↓ Bodyweight gain; ↑ relative liver and kidney weight. **5010 mg/m^3**: ↓ Bodyweight gain; ↑ Relative liver and kidney weight clinical signs. **Pups:** **503 mg/m^3**: ↑ Relative adrenal weight (M). **1001 mg/m^3**: ↑ Relative adrenal weight (M). **3008 mg/m^3**:↓ Bodyweight gain (M; pnd 22-25): ↓ platelets (F). **5010 mg/m^3**: ↓ Bodyweight gain (M: pnd 22-29, F: pnd 22-25); ↓ Absolute brain weight (M,F), ↑ relative adrenal weight (M); ↓ platelets (M,F), ↑ gamma-glutamyl transferase (M,F); ↓ glucose (M,F).	Huntingdon Life Sciences, 1999
503 1257 2514	6h/7d/wk for gestation and lactation. Whole body.	CD Rat	**Dam:** See table in Section 4. **Pup:** **Developmental NOEL=1258** **2514 mg/m^3:** ↓ Weight gain during lactation period.	WIL Research Laboratories (2001)[a]

[a]Reproductive effects for this study are summarized in Section 4.
↑=Increased Effect; ↓=Decreased Effect; M=Male, F=Female.

4.0 REPRODUCTIVE TOXICITY

4.1 Human Data

In 1998, NIOSH conducted a health hazard evaluation at a plant where a 1-BP-containing spray adhesive was used in the manufacture of seat cushions (Reh, 2000). Forty-three employees (34 females and 9 males), whose exposure levels were classified as low (117 ppm), medium (170 ppm), or high (197 ppm), were asked about reproductive problems. One employee (sex not specified) in the low exposure group reported seeing a doctor for reproductive/fertility problems and two males and one female in the low or mid exposure groups said they could not have a child after trying for one year. NIOSH noted that their ability to detect reproductive or fertility problems was limited by the small sample size and personal nature of the questions asked. An analysis of blood samples for complete blood count was also conducted and is discussed in Section 2.

Strength/Weaknesses: This pilot data is too preliminary to be of much use. The survey analysis was based on only 43 of 70 workers. Considering that about 10% of couples in the US seek medical attention for infertility, 3 of 42 workers reporting possible fertility problems is not unexpected.

Utility (Adequacy) for CERHR Evaluation Process: The study is not useful except to point to the need for a well-designed human study with adequate exposure information and adequate power to detect an effect (i.e., one that monitors menstrual cycles and examines semen quality and serum hormones). A well-designed study would also include collection and analysis of potentially confounding factors.

4.2 Experimental Animal Toxicity

In a study sponsored by the Brominated Solvents Consortium, WIL Research Laboratories (2001) evaluated the potential adverse effects of 1-BP whole-body inhalation exposure in F_0 and F_1 parental rats; reproductive capabilities were examined in the F_0 and F_1 generations and neonatal survival, growth and development were evaluated in F_1 and F_2 offspring. In this 2-generation reproductive toxicity study, groups of 25 male and female Crl:CD(SD)IGS BR rats were exposed to filtered air or 100, 250, 500, or 750 ppm [0, 503, 1257, 2514, 3771 mg/m^3] 1-BP vapors (99.8% purity) for 6 hours/day, 7 days/week. Chamber concentrations were measured. Exposure of F_0 rats commenced at 7 weeks of age and F_1 rats began direct exposure at weaning. Exposures were conducted for at least 70 days prior to mating. Females were not exposed on pnd 0-4 and only they, not their litters, were exposed during pnd 5-21. Therefore, offspring (litters) were indirectly exposed to the test chemical *in utero* and through nursing. In addition, the F_1 pups selected randomly for propagation of F_2 litters were directly exposed from pnd 22 forward. Concentrations of 1-BP were monitored inside inhalation chambers. Results in treated animals were compared to both air control and historical control data from WIL Research Laboratories. Statistical analyses were stated to generally be conducted using two-tailed tests for a minimum significance of p=0.05. Most data were analyzed by one-way ANOVA with Dunnetts test. Exceptions were Chi-square test with Yates correction factor for parental mating and fertility indices; Kruskall-Wallis test with Mann-Whitney U-test for sperm motility, % normal sperm, pup sex at birth, proportional postnatal survival; and Fisher's Exact test for histopathological findings. The study was stated to have been conducted in compliance with Good Laboratory Practices (GLP).

Numerous systemic effects were observed. Significant reductions in cumulative weight gain were noted in F_0 males and females of the 750 ppm group throughout the study. Significant reduction in weight gain was also seen in F_0 and F_1 males in the 500 ppm group and reduced body weight gain was also seen in F_0 and F_1 females in the 500 ppm group during gestation and lactation. Significant reductions in absolute but not relative brain weight were seen in F_1 males (≥100 ppm), F_0 males (≥250 ppm) and F_0 and F_1 females (≥500 ppm); however, no histopathological lesions were observed. Significant increases in relative liver weight were seen in F_0 males and F_1 males and females (≥500 ppm) and F_0 females (750 ppm). Exposure-related hepatic lesions that increased in severity and incidence according to dose consisted of minimal to mild centrilobular hepatocellular vacuolation and increased glycogen. Those hepatic effects were observed in F_0 males and F_1 males and females exposed to 250 ppm and higher and F_0 females exposed to 500 ppm and higher. No effects on kidney weight were reported but minimal to mild pelvic mineralization and secondary transitional epithelial hyperplasia were observed in F_1 females exposed to ≥250 ppm and F_0 and F_1 males and females exposed to ≥500 ppm. Absolute thymus weights were increased in F_1 males exposed to ≥250 ppm, but no histological lesions were reported.

Reproductive effects are outlined in Table 4-1. Evidence of compromised reproductive performance was noted in F_0 rats of all dose groups. The length of estrous cycles (monitored for 21 days prior to mating) was increased in F_0 rats in the 250, 500 and 750 ppm groups. The mating index was significantly lower in the F_0 750 ppm group. An increased time to coitus in the F_0 500 and 750 ppm groups was not statistically significant but exceeded historical control values. Fertility index was significantly lower in the F_0 500 and 750 ppm groups and none of the females in the 750 ppm group became pregnant. 1-BP treatment had no effect on gestation length or complications during delivery. Litter size and numbers of implantation sites were significantly reduced in the 500 ppm group. At necropsy, significant reductions in F_0 absolute reproductive organ weights included ovary (≥ 500 ppm), epididymis (≥250 ppm), prostate (≥250 ppm), seminal vesicle (≥500 ppm), and pituitary (750 ppm). Significant effects on relative organ weights were only observed in the 750 ppm group and included an increase in left testis weight and reductions in caudal epididymides and ovary weight. Organs evaluated histologically included ovaries and testes; the latter tissue and epididymides were preserved in Bouins fixative. Ovarian lesions in F_0 rats included a dose-related reduction in corpora lutea in the 500 and 750 ppm groups that achieved statistical significance in the higher dose. Also noted in the 750 ppm group were increased follicular cysts and interstitial cell hyperplasia. In males, a slightly increased incidence of seminiferous tubule degeneration was not considered treatment related by the study authors since lesions in 4 of the 6 affected rats were of minimal severity. An analysis of sperm from F_0 rats revealed significant reductions in morphologically normal sperm and in sperm motility at 500 and 750 ppm and reduced sperm counts at 750 ppm.

The F_1 rats were evaluated for postnatal growth, development, and survival. A slight, but significant reduction in pup viability on pnd 14-21 in the F_1 500 ppm group was not considered of sufficient magnitude to be biologically significant and study authors concluded that there were no effects on pup survival. Significant reductions in F_1 litter weight gain were noted in males of the 250 ppm group (pnd 21-28) and 500 ppm group (pnd 4-7, 7-14, and 21-28). A significant reduction in F_1 female weight gain was only noted in the 500 ppm group on pnd 21-28. The age of balanopreputial separation was significantly increased in the F_1 500 ppm group but authors attributed that effect as secondary to reduced weight gain in that group. 1-BP treatment had no effect on the age of attaining vaginal patency. 1-BP exposure in the F_1 animals was initiated on pnd 22 and 25 rats/sex/group in the control and 100-500 ppm groups were selected for mating.

The mating experiment was conducted as described for the F_0 rats. Increased estrous cycle lengths in the 250 and 500 ppm F_1 groups were within ranges of historical controls but were attributed by authors to 1-BP treatment. No significant effects were noted for F_1 fertility or mating indices, days to mating, gestation length, or birthing complications. However, authors noted that non-significant and non-dose related reductions in fertility indices in the F_1 100, 250, and 500 ppm groups (68, 64, 72%, respectively) were below fertility indices of historical controls (~90%). Mean numbers of implantation sites were reduced in the F_1 250 and 500 ppm groups with statistical significance achieved at the higher dose level. Live litter size was significantly decreased at 500 ppm. Ovarian lesions included increases in the number of follicular cysts and incidence of interstitial cell hyperplasia in the F_1 500 ppm group. Absolute epididymis and pituitary weight were significantly reduced in the F_1 500 ppm males. Lesions observed in testes were considered minimal and their incidence was not altered significantly by treatment, although there appeared to be a trend. Other male reproductive organs were histologically normal. F_1 sperm motility, and the numbers/percentages of morphologically normal sperm were significantly reduced at 500 and 750 ppm. A significant reduction in F_1 sperm motility at 250 ppm was not considered to be dose-related since the value exceeded that of historical controls. F_2 rats were only evaluated for postnatal growth and survival to pnd 21. Postnatal weight gain in males and females was significantly reduced in the F_2 500 ppm group. Survival was unaffected.

Strength/Weaknesses: This is a Comprehensive study conducted under GLP and meeting specifications of EPA's harmonized reproductive test guidelines. It includes indices of puberty as measures for reproductive development, and sperm measures as indices of testicular and epididymal function. This allows effects on reproductive organ function to be detected in the absence of altered reproductive performance. Results provide convincing evidence that 1-BP is a reproductive toxicant.

Results suggest that the female is the more sensitive sex in that alterations in estrous cycle in F1 females were seen at 250 ppm while effects on sperm measures were not observed at this dosage. (However, it's not clear why estrous cycle length data were not subjected to statistical analysis). Possible interpretation could be discussed – that 1-BP caused subfertility in both males and females that may account for decreased fertility at 500 ppm and infertility at 750 ppm. [The Expert Panel notes a need to discuss these results in light of reduced weight gain (general toxicity?) seen especially at 750 ppm, the dose that resulted in infertility.

A point could be made that adverse effects at 500 ppm were very consistent across generations, so there is no evidence for a transgeneration effect, or increased susceptibility during perinatal or pubertal stages.

Lack of statistical significance for vaginal opening ignores a trend towards delayed vaginal opening in F1 females. This might be significant with different statistical analysis (and would be consistent with estrous cycle perturbations observed in adult females).

Sperm motility is poorly defined (p. 49 of study). The HTM-IVOS sperm analysis system used by study authors permits the user to define "motile" and "progressively motile" sperm based on cut-offs for several settings. These should be specified so that the reader can tell whether the test distinguished between sperm with typical progressive motion from those that might have poor, non-progressive motion (Seed et al., 1996). Likewise, sperm count methods are poorly described (p. 50 of study): when made with the HTM-IVOS, the important unit is number of fields counted (as this determines the volume assessed and is necessary to derive the sperm count), and not a minimum number of sperm counted. Nevertheless the data compare favorably with published values.

Criteria for scoring histology are not provided (p. 55 of study). Some animals at 500 and 750 ppm seemed to be more than "minimally" affected, especially as they contained at least some tubules with "Sertoli cell only." One would expect to see histologic evidence of abnormal spermatogenesis based on significant reduction of sperm counts in the 750 ppm group. The Panel has suggested that study authors may want to consider redoing the statistical analysis for incidence of testicular pathology.

The report has a section titled "Discussion and conclusions" but it is a summary, with no real discussion of the data or significance of the findings. For example, decreased weights of epididymis, prostate and seminal vesicle could be indicative of lower weight gain in offspring, or could be indicative of an endocrine effect. Although not required by the test guidelines, serum hormone measures would be valuable in this case. Also, significant changes in sperm measures appeared to occur in the absence of histological lesions, but this may be due to the manner in which the histology data was analyzed.

Utility (Adequacy) for CERHR Evaluation Process: This is an excellent study for hazard identification and is definitely adequate for the CERHR evaluation process. However, results need to be synthesized and interpreted.

Table 4.1. Major Effects Observed in a Two-Generation Reproductive Toxicity Study in Sprague Dawley Rats by WIL Research Laboratories (2001)

Number[a]	Dose (ppm)	Effects in F_0 Parents[d]	Effects in F_1 Offspring [F_2 Offspring] [d]
25	0		
25	100	No effects.	
25	250	↓ Epididymis and prostate weight ↑Estrous cycle length (4.5 vs 4.2 days)	↓F_1 weight gain on pnd 21-28 (M). ↑Estrous cycle length. (4.9 vs 4.5 days).[c]
25	500	↑Estrous cycle length (5.5 vs 4.2 days).[c] ↓Fertility (52 vs 92%). ↓Litter size (n=8.3 vs 14.4). ↓Implantation sites (9.0 vs 15.3). ↓Normal sperm (98.2 vs 99.7%) and sperm motility (72 vs 87%). ↓ Ovary, epididymis, prostate, and seminal vesicle weight.	↓F_1 weight gain through pnd 28 (M) and pnd 21-28 (F). ↑Estrous cycle length (5.1 vs 4.5 days).[c] ↓Implantation sites (9.8 vs 15.5).[b] ↓Litter size (8.6 vs 14.5). ↑Ovarian lesions. ↓Normal sperm (95.3 vs 99.5%) and sperm motility (74.4 vs 88.9%).[b] ↓ F_1 epididymis and pituitary weight. [↓F_2 postnatal weight gain on pnd 4-21] No effect on F_1 or F_2 postnatal survival or F_1 vaginal opening, mating indices, gestation length, parturition, or testicular lesions.
25	750	↓ Weight gain. ↑ Estrous cycle length (5.6 vs 4.2 days).[c] ↓ Mating (68 vs 96%). ↑ Pre-coital interval (4.8 vs 3.4 days).[b] No conceptions. ↓ Corpora lutea (n=11 vs 3). ↑Ovarian lesions. ↓ Normal sperm (90.6 vs 99.7%), sperm motility (53 vs 87%). ↓Sperm count (370 vs 472x10^6/gram tissue). ↓ Ovary, epididymis, prostate, seminal vesicle, and pituitary weight. No effects on gestation length or parturition.	No F_1 rats available due to complete infertility in F_0 rats.

Protocol: Inhalation exposure to 1-BP from 70 days prior to mating, during gestation and most of lactation in F_0 and F1. Reproductive function evaluated in F_0 and F_1; postnatal mortality and growth evaluated in F_1 and F_2 litters.
Notes: M=Male; F=Female; ↑,↓=Statistically significant increase, decrease.
[a]Number of F_0 and F_1 male and female pairs, except that no F_1 offspring were available at 750 ppm.
[b]Numerical evidence of dose trend at 250 and 500.
[c]No statistical analyses conducted.
[d]See synopses for details about systemic effects.

A study by Ichihara et al. (2000b) examined the dose response of 1-BP-induced testicular toxicity including sperm measures (motility/morphology) and detailed testicular histology (testes fixed in Bouin's and stained with period acid Schiff's reagent). In the examination of testicular histology,

subtle changes in seminiferous tubule cell associations, similar to those recommended by Creasy (1997), were evaluated. These included enumeration of spermatogenic cells in stage VII tubules and elongated spermatids retained in stage IX-XI tubules (normally released at stage VIII). The rationale for this study included the increased use of 1-BP in industry and the previously reported reproductive toxicity induced by its isomer, 2-BP. Eight to nine, 10-week-old male Wistar rats (from the Shizuoka Laboratory Animal Center) were exposed to air or 200, 400, or 800 ppm [1006, 2012, or 4025 mg/m^3] 1-BP vapors (99.81% purity) for 8 hours/day for 12 weeks. The maximum dose in this study was selected based on observations in previous studies that exposure to 1,000 ppm resulted in debilitation. Chamber concentrations of 1-BP were measured and reported. At the end of the exposure period the rats were sacrificed and necropsied. Data were evaluated by one-way ANOVA followed by Dunnett's method. Reproductive effects are discussed here while other systemic effects are discussed in Section 2. Table 4-2 lists findings of this study. Significant reductions in absolute organ weights were observed for seminal vesicles (≥200 ppm), epididymides, pituitary (≥400 ppm), and prostate (800 ppm). Significant reductions in relative organ weights were noted in seminal vesicles (≥200 ppm), and epididymides (800 ppm). Body weight gain was reduced in the 400 and 800 ppm groups. Histopathological changes were observed in the epididymides, prostate, and seminal vesicles of the 800 ppm group. Epididymides had reduced duct cavity diameter, wider interstitial space, increased epithelial cell height and contained neutrophils or degenerated epithelial cells. Prostate and seminal vesicles had reduced alveoli size and degenerated cells were observed in the seminal vesicle cavity. Histological evaluation of testes revealed vacuolated seminiferous epithelium in 2 of 9 rats of the 800 ppm group. The numbers of retained elongated spermatids in stages IX, X, and XI were significantly increased in 400 and 800 ppm groups and a significant increase in degenerating spermatocytes in stage VII was seen in the 800 ppm group. Sperm quality was also affected as observed by significant reductions in sperm count and motility and increases in tailless sperm at ≥400 ppm. At 800 ppm a significant increase in sperm with abnormal heads (banana-like or straight) was observed. Table 4-2 includes values for sperm parameters. Plasma testosterone level was significantly reduced in the 800 ppm group, but there were no changes in follicle stimulating hormone (FSH) or luteinizing hormone (LH) levels. The presence of retained elongated spermatid during the postspermiation periods (stages IX-XI) led authors to conclude that the likely mode of 1-BP toxicity results in failure of spermiation. Authors stated that this pattern of toxicity differs from that of 2-BP which has been reported to target spermatogonia.

Strength/Weaknesses: A strength of this study is the thorough evaluation of testicular effects of 1-BP including detailed histology, sperm measures, and serum hormones. The exposure period is sufficiently long to see effects on all spermatogenic stages, and the range of doses is sufficiently wide to determine a no effect level and begin to see systemic effects on body weight. Enumeration of spermatogenic cell types in seminiferous tubule cross sections allowed conclusions about sensitive cell types and/or stages. The conclusion that the main effect in testis is spermatid retention beyond Stage VIII is indicative of Sertoli cell effect and/or possible effect on endocrine support of spermatogenesis. Decreased testosterone levels in the high dose group coupled with decreased weights of testosterone-dependent organs (most consistently the seminal vesicles) are consistent with the latter hypothesis, as is observed decrease in sperm quality (motility/morphology). Retained spermatids may explain decreased numbers of sperm in the epididymides.

A weaknesses of the study is that relatively low numbers of animals per group (9-10) limits the power of the study to detect an effect. For example, lower and more variable serum testosterone level might obtain statistical significance if more animals were assessed.

Utility (Adequacy) for CERHR Evaluation Process: This study is particularly useful for characterizing effects of 1-BP in males since it includes detailed histology with quantification of germ cells and serum hormones. It has limited usefulness for hazard ID since it does not include a fertility assessment, but is a valuable adjunct to other studies.

Table 4-2. Major Effects in Reproductive Toxicity Study in Wistar Rats by Ichihara et al. (2000b).

Number/ Dose	Dose (ppm)	Effects
8	0	
9	200	↓ Absolute seminal vesicle weight. ↓ Relative seminal vesicle weight.
9	400	↓ Absolute seminal vesicle, epididymides, and pituitary weight. ↓ Relative seminal vesicle weight. ↑ Retained elongated spermatids (1.3 vs 0.49/tubule). ↓ Sperm count (588 vs 792x10^6/g cauda). ↓ Motile sperm (67 vs 83%). ↑ Tailless sperm (18 vs 4%). ↓ Body weight gain. ↑ Relative liver weight. ↓ Mean corpuscular hemoglobin concentration.
9	800	↓ Absolute seminal vesicle, epididymides, pituitary, and prostate weight. ↓ Relative seminal vesicle and epididymides weight. ↑ Histological changes in epididymides, prostate, and seminal vesicles. ↑ Retained elongated spermatids (4.8 vs 0.49/tubule). ↑ Degenerating spermatocytes (0.6 vs 0.04/tubule). ↓ Sperm count (240 vs 792x10^6/g cauda). ↓ Motile sperm (25 vs 83%). ↑ Tailless sperm (36 vs 4%). ↑ Abnormal sperm (100 vs 1%). Vacuolated seminiferous epithelium in 2/9 rats. ↓ Plasma testosterone (2.9 vs 4.5 ng/ml) with no change in LH or FSH. ↓ Body weight gain. ↑ Relative and absolute liver weight; ↓ absolute spleen weight. ↑ Histological changes in liver. ↑ Mixed cell volume. ↓ Mean corpuscular hemoglobin concentration.
Protocol: Ten week old male rats exposed to 1-BP vapors for 8 hours/day for 12 weeks. Notes: ↑, ↓: Statistically significant increase, decrease.		

In two other studies (Kim et al., 1999b; Yu et al., 2001), testes were examined microscopically and no adverse effects were reported. In the Kim et al. (1999b) study, Sprague-Dawley rats inhaled 1,800 ppm 1-BP for 6 hours/day, 5 days/week, for 8 weeks. Testes were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned and stained with hematoxylin-Eosin and/or PAS hematoxylin. In the Yu et al. (2001) study, male Wistar rats were exposed to 1,000 ppm 1-BP vapors (99.4% purity) for 8/hours/day for 5 or 7 weeks. Kim et al. (1999b) reported an increase in relative weight of ovaries, but no ovarian lesions were observed. Additional details of these two studies are included in Section 2.

Strength/Weaknesses: The experimental design could allow comparison of relative effects on gonads and blood. However, there is no indication that testes (or ovaries) were examined for subtle effects such as retained spermatids or vacuolated Sertoli cells, i.e. it is doubtful that testes were evaluated in sufficient detail to detect changes seen in the other studies. Lack of effect could also be due to the shorter duration of exposure, but 7-8 weeks should be long enough to affect spermiation and sperm counts. Increased relative weights of testes and ovaries could simply be due to body weight depression without change in absolute gonad weights.

Utility (Adequacy) for CERHR Evaluation Process: This study is not useful for evaluating reproductive effects. It may be useful for comparing blood measures with other studies.

Two unpublished general toxicity studies also provide information about testicular effects. In a 28-day study, aspermatogenesis was noted in Sprague-Dawley rats exposed to 8000 mg/m^3 1-BP vapors (ClinTrials, 1997a). No testicular or ovarian lesions were observed in Sprague-Dawley rats exposed to up to 3000 mg/m^3 1-BP vapors for 13 weeks (ClinTrials, 1997b). In both studies, testes were fixed in Zenker's fluid. Complete details of these studies and a review of strengths, weaknesses, and utility is included in Section 2.

Saito-Suzuki et al. (1982) conducted dominant lethal studies in rats to determine the structure-activity relationships of 5 halogenated propanes. In addition to 1-BP (>98% purity) the following compounds were examined: 1,2,3-tribromopropane, 1,2-dibromopropane, 1,2,3-trichloropropane, and 1-chloropropane. Eleven-week-old male Crl: Sprague Dawley rats (n=15/group) were gavaged with 10% of the acute lethal dose of each compound in olive oil for 5 days. 1-BP was administered at a dose of 400 mg/kg bw. Olive oil was the negative control and 1,2-dibromo-3-chloropropane was the positive control (n=15/group). At 1-8 weeks after treatment, the males were mated weekly with untreated females. Data were analyzed using Fisher's Exact Method and the Mann-Whitney U test. 1-BP treatment had no effect on male fertility. Females (n=15/time period) were sacrificed 13-14 days after mating and examined for corpora lutea, implants, live embryos, and early and late embryonic deaths. 1-BP treatment increased the number of mean dead implants at 8 weeks following treatment but had no effect on the dominant lethal mutation index (live embryos per test female/live embryos per control females). The authors concluded that dominant lethal mutations were induced by propanes containing a halogen atom of bromine or chlorine on each carbon atom with bromine comprising 2 of the halogen atoms.

Strength/Weaknesses: This is a classic dominant lethal study showing that a relatively high dose of 1-BP (~maximum tolerated dose) does not induce dominant lethality. Other halogenated propanes serve as controls in that they are effective at lower dosages.

Utility (Adequacy) for CERHR Evaluation Process: This paper is important since it rules out 1-BP as a germ cell mutagen, and thereby rules out a mechanism of action exhibited by related halogenated propanes. The study also shows that short term (5 day) exposure at high levels do

not produce adverse effects sufficient to affect fertility, but it did not look for specific changes in testis/epididymis function.

4.3 Utility of Data

4.4 Summary of Reproductive Toxicity

There are insufficient data upon which to evaluate the reproductive toxicity of 1-BP in humans.

Reproductive studies, including a 2-generation study, were conducted in rats. This reproductive summary for rats first addresses female effects and then male effects noted in the composite of available inhalation studies. Lastly, effects on reproductive performance are addressed together for males and females in 2-generations. Major findings of these studies are included in Table 4-3.

There are sufficient data to indicate that repeated chronic inhalation exposure of female Sprague-Dawley rats to 1-BP at doses of 250 ppm (1,257 mg/m^3) and higher result in reproductive toxicity. Effects included a dose related increase in estrous cycle length at ≥250 ppm (1,257 mg/m^3) and follicular cysts and interstitial hyperplasia of ovaries at concentrations ≥2,514 mg/m^3 (500 ppm) (WIL Research Laboratories 2001). Reduced fertility and litter size was observed in the F_0 and F_1 generations but the experimental design did not permit differentiation as to whether these effects were due to reduced female or male fertility, or both. No ovarian lesions were observed in rats exposed to lower doses or for shorter time periods including 8,000 mg/m^3 for 4 weeks or 3,000 mg/m^3 for 13 weeks (ClinTrials, 1997b).

There are sufficient data to indicate that repeated inhalation exposure of male rats to 1-BP results in reproductive toxicity at doses of 500 ppm (2,514 mg/m^3) and higher. Effects in a 2-generation study included dose–related decreases in normal sperm and sperm motility in F_0 and F_1 generations at ≥500 ppm (2,514 mg/m^3) (WIL Research Laboratories, 2001). Decreased sperm count was also observed at the 750 ppm (3 771 mg/m^3) dose. Reduced fertility and litter size was observed in the F_0 and F_1 generations but the experimental design did not permit differentiation as to whether these effects were due to reduced female or male fertility, or both. Testicular toxicity was characterized in a subchronic inhalation study (Ichihara et al., 2000b). Histopathological changes were observed in epididymides, prostate and seminal vesicles at doses of 800 ppm (4,025 mg/m^3). The presence of retained elongated spermatid were increased at doses of 400 and 800 ppm (2,012 and 4,015 mg/m^3), as were reductions in sperm count and motility. Plasma testosterone levels were reduced at 800 ppm (4,025 mg/m^3) (Ichihara et al., 2000b). Examination of testes using standard histological methods revealed no testicular lesions in rats exposed for 7–13 weeks at concentrations ranging from 252–9055 mg/m^3 (Kim et al., 1999b; Yu et al., 2001; ClinTrials, 1997b). The Expert Panel doubts that testes were examined in sufficient detail to detect the changes reported by Ichihara et al. (2000b). The Expert Panel noted a conclusion by Ichihara et al. (2000b) that the main effect in testis is spermatid retention beyond Stage VIII; the Panel believes this may indicate possible effects on Sertoli cells or endocrine support of spermatogenesis.

The Expert Panel selected a NOAEL of 100 ppm (503 mg/m^3) for the 2-generation reproductive toxicity study (WIL Research Laboratories, 2001). The Expert Panel opined that reduced fertility in the 2-generation study was due to reproductive toxicity in both males and females since exposure to 2,515 mg/m^3 (500 ppm) increased estrous cycles length and compromised sperm quality (as discussed above in separate summaries for male and female rats). Further, the Panel

noted that the reproductive systems of females may be more sensitive since disrupted estrous cycles were also observed at the next lowest dose (1,257 mg/m^3); however a definite conclusion cannot be made since changes in estrous cycle length were not statistically analyzed. Lastly, the Expert Panel noted consistency of effects across the two generations and stated there was no evidence of increased sensitivity in developing rats exposed *in utero* and indirectly through mother's milk.

Table 4-3. Summary of Reproductive Toxicity Inhalation Studies

Concentration (mg/m^3)	**Exposure Regimen**	**Species/Strain**	**Dose: Effect[a]**	**Reference**
503 1257 2514 3771 (F_0 only)	6h/7d/10 wk prior to mating and during gestation and lactation. Whole body.	Male and female CD Rat	**NOAEL=503 mg/m^3** **1257 mg/m^3:** ↑Estrous cycle length; ↓epididymis and prostate weight (F_0). **2514 mg/m^3:** ↑Estrous cycle length; ↑ ovarian follicular cysts and interstitial cell hyperplasia (F_1); ↓ normal sperm and sperm motility; ↓ ovary (F_0), epididymis, prostate (F_0), seminal vesicle (F_0) and pituitary (F_1) weight;↓ fertility, implantation sites, and litter size; ↑ precoital interval. **3771 mg/m^3:** ↑Estrous cycle length; ↑ ovarian follicular cysts and interstitial cell hyperplasia; ↓ sperm count, normal sperm and sperm motility; ↓ ovary, epididymis, prostate, seminal vesicle and pituitary weight;↓ mating, ↑ precoital interval, and complete infertility.	WIL Research Laboratories (2001)
1006 2012 4025	8h/12 wk whole body.	Male Wistar Rats	**1006 mg/m^3:** ↓ Absolute and relative seminal vesicle weight. **2012 mg/m^3:** ↑ Retained elongated spermatids; ↓ sperm count and motility and ↑ tailless sperm; ↓ absolute seminal vesicle, epididymides, and pituitary weight and relative seminal vesicle weight. **4025 mg/m^3:** ↑ Retained elongated spermatids and degenerating spermatocytes; ↓ sperm count and motility and ↑ tailless sperm and abnormal sperm; vacuolated seminiferous epithelium in 2/9 rats; epididymis, prostate, and seminal vesicle lesions; ↓ testosterone; ↓ absolute seminal vesicle, epididymides, prostate, and pituitary weight and relative seminal vesicle and epididymides weight.	Ichihara et al. (2000b)

↑=Increased Effect; ↓=Decreased Effect; F_0=Effects observed only in F_0, F_1=Effects observed only in F_1.

5.0 SUMMARIES, CONCLUSIONS, AND CRITICAL DATA NEEDS

5.1 Summary and Conclusions of Reproductive and Developmental Hazards

5.2 Summary of Human Exposure

5.3 Overall Conclusions

5.4 Critical Data Needs

6.0 REFERENCES

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